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Case Report

Ascorbic acid deficiency impairs wound healing in surgical patients: Four case reports

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ABSTRACT

Background: Vitamin C or ascorbic acid (AA) is the antiscorbutic factor preventing scurvy. It is essential for collagen synthesis, serving as cofactor in the enzymatic conversion of procollagen into collagen.

Scurvy is regarded as something from the past; however, patients with low or subclinical levels of AA are frequently seen in our hospital. A subclinical deficiency will not often cause the display of the hallmark symptoms of scurvy, but this may lead to an altered collagen synthesis and have major implications for adequate wound healing, such as in the surgical field.

Case summary: AA was measured by HPLC using UV detection (Recipe) in a teaching hospital surgical patient group (n = 180) within a week pre- or post-surgery. Over a period of 21 months we found AA levels below the reference limit (25 umol/L) in 65 out of 180 patients (36%). Four patients described in detail initially showed poor wound healing. Their AA levels were 8, 4, and 19 umol/L respectively. After starting supplementation (1000 mg/day) a dramatic and fast recovery of extensive and complicated wounds was observed by patients and their clinician. Supplementation was ceased after the wounds were completely healed.

Conclusion: AA deficiency is not uncommon in the hospital population, especially in those at risk. Treating deficient patients with AA leads to swift improvement of the wound healing process post-surgery, thereby reducing the costs of extensive wound treatment and extended stay in hospital.

1. Introduction

Classically, major complications caused by AA deficiency are seen in scurvy patients; however, patients nowadays often do not display these hallmark characteristics. Individuals suffering from vascular disease, elderly people, pregnant women, smokers and substance abusers, and malnourished people are especially prone to AA deficiency. This is demonstrated by the four cases reported below. These patients were all at increased risk of developing an AA deficiency, which in turn resulted in poor wound healing. Treatment of these patients with AA resulted in a rapid improvement of wound healing.

2. Case report 1

A 59-year-old man underwent an exploratory laprotomy in our hospital for abdominal pain caused by diverticulitis, for which he received appendectomy and sigmoid colectomy. Postoperatively, he suffered twice from an abdominal wound dehiscence, which was surgically corrected (Fig. 1A), the second time with polyglactin mesh interposition, for which the wound was left open (wound size 30 × 25 cm). Unfortunately, the healing process did not show improvement, despite optimal wound care with alginate dressings (Fig. 1B and C). After 6 weeks with little result the patient was told to take AA suppletion of 1000 mg dd orally. No changes were made in his wound dressing regime. Healthy granulation tissue was seen after 2.5 weeks, and the wound size was reduced to one third of its original size (Fig. 1D and E). 2.5 months after start of AA supplementation the wound was fully closed (Fig. 1F). As a result of this case, we decided to conduct a retrospective study in a group of surgical patients with poor wound healing that had their AA measured. Three additional cases are described in detail below.

3. Case report 2

A 79-year-old woman with an extensive medical history, including asthma, severe chronic obstructive pulmonary disease, degenerative spondylolisthesis, total left and right hip replacement, rheumatoid arthritis, and chronic venous insufficiency (grade IV) was admitted to the Meander Medical Center with severe leg

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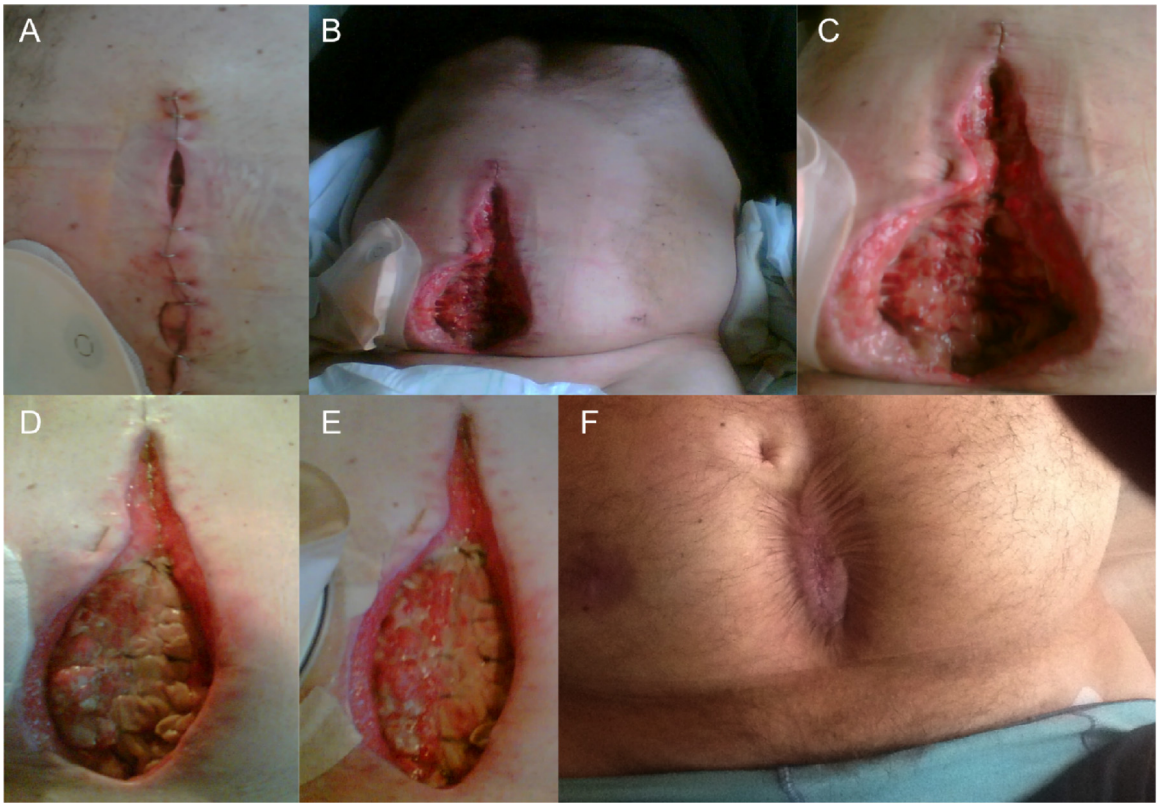

Fig. 1. Post-operation pictures taken by the patient showing an abdominal wound dehiscence and inadequate wound healing (A, B, C), and after ascorbic acid supplementation showing healthy granulation tissue (D, E) and full closure after 2.5 months (F).

ulcers. She underwent a surgical intervention to remove necrotic tissue and her wounds were treated by pinch grafting. Her wounds were dressed post-operatively with Aquacel Ag and dressings were changed when necessary. Unfortunately her post-operative wounds remained ulcerative and showed no progression toward healing. Her treatment was continued with Fluocinonide and Aquacel Ag three times weekly, and her wounds were additionally dressed with foam dressing, and after a month of treatment her wounds seemed to heal accordingly. After two months, however, she returned with a new wound, which was treated with a foam dressing and Cutimed Sorbact. After 9 months of extensive and optimal wound care with disappointing results her vitamin status was measured. Vitamin D (100 nmol/L), B12 (240 pmol/L) en folate (10.5 nmol/L) levels were in the normal range, but her AA level was very low (8 umol/L, reference range 25–85 umol/L). Other laboratory parameters showed a slight normocytic anemia, but no further abnormalities. The patient was immediately started on AA supplementation, 1000 mg a day (effervescent tablet), and after 3 to 4 weeks the patient noticed a significant improvement. After 8 weeks her ulcers were completely healed and supplementation was discontinued.

4. Case report 3

A second case involves a 68-year-old woman, again with an extensive medical history, including Crohn's disease, hypertension, diabetes type 2, cardiovascular disease, and thyroiditis as a result of amiodarone use. She had undergone an ileocecal resection correcting a perforation of the terminal ileum and as a result developed a severe case of peritonitis. Her post-surgery AA level was found to be 4 umol/L; other vitamins measured were active vitamin B12 75 pmol/L (ref. >21 pmol/L), B1 was 179 nmol/L (ref. 88–157 nmol/L), B6 was 83 nmol/L (ref. 35–110 nmol/L), and D3 27 nmol/L (ref. 50–132 nmol/L). Due to her Crohn's disease she had a slightly decreased albumin level (23 g/L, ref. 29–46 g/L), and a history of anemia of the chronic disease. After 2 months she had to undergo another emergency laparotomy because of an anastomotic leakage, resulting in the construction of a loop ileostomy. Surprisingly, a poorly healed laparotomy closure from her previous surgery was observed and the abdominal fascia hardly showed any closure at all. She also suffered from multiple perforations of the transverse colon for which a wedge resection and side-to-side anastomosis was performed. Shortly after, she was started on 2×500 mg AA intravenously during two weeks and 2×500 mg AA orally for two weeks after which no further surgery was needed.

5. Case report 4

The last patient being discussed is a 56-year-old man who was diagnosed with thromboangiitis obliterans (Buerger disease) as a result of nicotine abuse. He suffered from a deep, indolent, and ulcerative wound on the lateral surface of his right ankle (Fontaine stage IV). The wound was ischemic due to arterial insufficiency caused by his disease, and was intensely painful. Furthermore, a wound culture showed the presence of several bacteria (*Staphylococcus aureus*, *Streptococcus dysgalactiae*, *Pseudomonas aeruginosa*, and *Escherichia coli*). Unfortunately, no revascularization surgery was possible, because of far advanced vascular damage to his lower leg arteries. The patient was told to quit smoking and was started on 1 ng/kg/min iloprost (prostacyclin analogue) i.v. therapy for a total of three weeks in order to improve wound healing by relieving ischemic symptoms. In the first week of treatment his laboratory results showed a low AA level of 19 umol/L. Vitamin B12 (202 pmol/L), folic acid (8.4 nmol/L), vitamin D (90 nmol/L), and other laboratory parameters (hemoglobin, platelets, creatinine, CRP) were normal. This

prompted us to start with AA supplementation (500 mg, 2 dd). In one study comparing iloprost i.v. (1 ng/kg/min for 28 days) versus placebo treatment in Buerger disease patients, a complete healing rate of 62% *vs*. 41% respectively was observed at week 4 and 85% *vs*. 52% respectively at week 24 [1]. Our patient showed a full recovery after 3 weeks from a very deep and infected ulcer with this combination therapy of iloprost and AA.

6. Discussion

In our population of surgical patients (n = 180) we measured AA levels (HPLC using UV detection [Recipe kit], average cost per AA blood analysis €20,–/$22,–), because they displayed poor wound healing, despite adequate wound care. In 65 out of 180 patients (36%) AA levels were below the reference limit of 25 umol/L, demonstrating a significant prevalence of AA deficiency in our pilot hospital population.

As has been elaborately demonstrated in previous studies, AA plays a pivotal role in collagen synthesis, where it catalyzes the conversion of procollagen to collagen by substitution of a hydroxyl group for a hydrogen atom thereby acting as a reducing agent [2].

Dermal wound healing consists of three stages, i.e. connective tissue matrix deposition, contraction and epithelialization. This is preceded by a phase of hemostasis and inflammatory activation. During tissue matrix deposition, collagen, proteoglycans and attachment proteins are deposited to create a new extracellular matrix. The so-called myofibroblasts are responsible for contraction and are dependent on AA for the production collagen [3]. Epithelialization in turn also depends on AA, as this high metabolic process requires increasing amounts of nutrients and oxygen. Hypoxia-inducible factor-1a (HIF-1α) is therefore upregulated by vascular endothelial cells to increase angiogenesis by regulating vascular endothelial cell growth factor (VEGF) [4]. The healing process comprises an interplay of fibroblasts, epithelial cells, cytokines, and immune cells. Neutrophils and specialized macrophages play an important role in removing bacteria and tissue debris. In order to do so, they need to phagocytize and break down these harmful pathogens for which it is believed they need AA [5]. In fact, circulating white blood cells contain 10–30 times the plasma concentration of AA [6]. By adding the effect on inhibition of reactive oxygen species (ROS) formation in tissue cells, it is easy to see how AA deficiency could lead to ineffective wound healing [7].

AA is water-soluble and absorbed in the distal small intestine, where an average dose of up to 200 mg/day can be completely absorbed [8]. With higher doses given orally the relative absorption decreases. Dietary reference intakes for AA have been established at 90 mg for men and 75 mg for women [9]. Daily ingestion of at least 60 mg of AA should result in a body pool of 1500 mg [10]. A minimum of 45 mg/day should prevent scurvy in a healthy individual; correcting an AA deficit in scurvy patients takes an oral intake of at least 100 mg three times a day [11]. A meta-analysis of 44 clinical trials has shown a significant positive effect of AA on endothelial function when taken at doses greater than 500 mg per day. It was also found that the effect of supplementation appeared to be dependent on health status, with stronger effects in those at higher cardiovascular disease risk [12].

There is still no consensus about the therapeutic effects and dosage of AA, and several randomized control trials (RCTs) have shown no effect of antioxidant supplement on mortality and morbidity outcomes [13]. With regard to wound healing only two RCTs have been conducted [14,15]. Statistical analysis of both trials in this review showed that there was no evidence of a benefit of oral supplementation with AA (500 mg 2dd) on pressure ulcer healing [16].

In the first study by Taylor et al. [14] AA levels in both groups were on average not deficient (24 and 22 μg/10^8 leukocytes; deficiency is defined as <18 μg/10^8 leukocytes). Only 3 individuals in the placebo group and 2 in the AA intervention group showed an AA level lower than 18 μg/10^8 leukocytes. In the second study by ter Riet et al. [15] 37% of the ascorbic intervention group and 49% of the control group were not deficient and the control group received supplementation as well (10 mg AA 2dd orally).

In our three cases, concentrations well above the required dose of AA for treating scurvy were given, and for these and other cases a rapid improvement of wound healing within a few days to weeks after starting AA therapy was seen. Noteworthy, the route of administration might also have implications for its therapeutic effect. As oral doses exceed 200 mg the relative absorption decreases, excretion in urine increases, thereby reducing the bioavailability of AA [17].

This said, evidence from our cases shows that oral administration does have the potential to induce the regenerating properties of AA. Most likely, it is also dependent on the AA tissue storage prior to administration, and more importantly, pathological and other events (e.g. surgery) that trigger rapid AA loss.

7. Conclusion

Regarding the cases presented here, orally administered doses of ascorbic acid supplemented to patients with a preexisting deficiency, improved wound healing drastically. Furthermore, the oral administration of these doses of ascorbic acid is not harmful to patients, due to the tight control of its absorption and urinary excretion. Other, important benefits are the low costs of ascorbic acid supplementation together with the likely reduction of expenses caused by extensive wound care. It should therefore be considered to supplement patients suffering from poor wound healing with at least 2×500 mg or 1000 mg a day until the healing process is finished. If a patient needs to undergo surgery while being deficient, it is suggested that he/she should start supplemention with ascorbic acid post-surgery, during a normoxic state to prevent possible damage caused by its pro-oxidant effects, although evidence for its harmful effects seems largely hypothetical. One should keep in mind that such invasive procedures, even more if accompanied by severe infections or sepsis, could lead to a detrimental depletion of ascorbic acid storage. Finally, we recommend to carefully monitor patients for an ascorbic acid deficiency (signs and symptoms as well as measuring plasma ascorbic acid levels) pre- and post-surgery to prevent future cases like these, especially in those patients who are at risk for having a pre-existing ascorbic acid deficiency, and those suffering from vascular disease. Our cases demonstrate that treating deficient patients with ascorbic acid leads to swift improvement of the wound healing process post-surgery, thereby reducing the costs of elaborate wound treatment and extensive stay in hospital.

The work described here has been reported in line with the CARE criteria [18].

Ethical approval

The study was performed according to the medical ethical regulations of the Meander Medical Centre.

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Author contribution

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Ms Bikker had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest statement

The authors state that there are no conflicts of interest.

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